Is Alexithymia Associated with High Disease Activity in Rheumatoid Arthritis?

Romatoid Artritte Aleksitimi Yüksek Hastalık Aktivitesi ile İlişkili Midir?

Alexithymia and Rheumatoid Arthritis

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Özet

Amaç: Romatoid artritli hastalarda aleksitimi ve hastalık aktivitesi arasındaki ilişkiyi araştırmak. Gereç ve Yöntem: Romatoid artrit tanılı toplam 97 kadın hasta çalışmaya alındı. Öncelikle, hastalar eşik değeri 61 olan Toronto Aleksitimi Skalası-20 (TAS-20) kullanılarak aleksitimik ve aleksitimik olmayanlar olarak iki gruba ayrıldı. Ardından, aleksitimik olmayanlar tertil değerler kullanılarak düşük-normal, orta-normal ve yüksek-normal olmak üzere üç gruba ayrıldı. Hastalık aktivitesi DAS28-ESR (Disease Activity Score with 28 joints using erythrocyte sedimentation rate) ile belirlendi. Hasta tarafından bildirilen bileşenlerin hastalık aktivitesine katkısını anlamak için ise DAS28-ESR'den türetilen ve DAS28-P [Disease Activity Score in 28 joints attributable to Patient-reported Components (tender joint count and patient global assessment of disease activity)] olarak isimlendirilen bir indeks kullanıldı. DAS28-P, DAS28-ESR'nin hassas eklem sayısından ve hastalık aktivitesinin hasta tarafından global değerlendirmesi skorundan oluşan kısmının total DAS28-ESR skoruna oranı olarak hesaplandı. TAS-20 skor grupları arasında DAS28-ESR ve DAS28-P bakımından farklılıklar çalışıldı. Bulgular: Doksan yedi hastanın 28'i (%28.8) aleksitimik olarak sınıflandırıldı. Ortalama DAS28-ESR skoru, aleksitimik grupta, düşük-normal TAS-20 skorlu gruptan anlamlı olarak daha yüksekti (p=0.004). Ortanca DAS28-P skoru, aleksitimik grupta, düşük-normal ve orta-normal TAS-20 skorlu gruplardan anlamlı olarak daha yüksek bulundu (sırasıyla, p=0.001 ve p=0.015). Ortanca DAS28-P skoru ayrıca, yüksek-normal TAS-20 skorlu grupta, düşük-normal TAS-20 skorlu gruptan anlamlı olarak daha yüksekti (p=0.047). Tartışma: Yüksek hastalık aktivitesine sahip hastalarda aleksitimi varlığı karıştırıcı bir faktör olabilir.

Anahtar Kelimeler

Aleksitimi; Hastalık Aktivitesi; Romatoid Artrit

Abstract

Aim: To investigate the association between alexithymia and disease activity in patients with rheumatoid arthritis. Material and Method: A total of 97 female patients diagnosed with RA were enrolled in the study. First, the patients were classified into two groups as alexithymics and non-alexithymics according to the Toronto Alexithymia Scale-20 (TAS-20) threshold score of 61. Subsequently, non-alexithymic patients were divided into three groups according to tertile values as high-normal, middle-normal, and low-normal. Disease activity was determined by the Disease Activity Index with 28 joints using erythrocyte sedimentation rate (DAS28-ESR). To understand the contribution of patient-reported components to DAS28-ESR, a DAS28-ESR-derived index called DAS28-P [Disease Activity Score in 28 joints attributable to Patient-reported Components (tender joint count and patient global assessment of disease activity)] was used. The DAS28-P index was calculated as the ratio of the fraction of the total DAS28-ESR score contributed by the tender joint count and patient global assessment of disease activity score to total the DAS28-ESR score. Differences across TAS-20 score groups for DAS28-ESR and for DAS28-P were studied. Results: Twenty-eight of 97 patients (28.8%) were classified as alexithymic. The mean DAS28-ESR score was significantly higher in the alexithymic group than in the low-normal TAS-20 score group (p=0.004). The median DAS28-P score was significantly higher in the alexithymic group than in the low-normal and middle-normal TAS-20 score groups (p=0.001, p=0.015, respectively). The median DAS28-P score was also significantly higher in the high-normal TAS-20 score group than in the low-normal TAS-20 score group (p=0.047). Discussion: In patients with high disease activity, the presence of alexithymia may be a confounding factor.

Keywords

Alexithymia; Disease Activity; Rheumatoid Arthritis

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Introduction

Pain is the most predominant symptom of rheumatoid arthritis (RA). In addition to pain due to synovial inflammation, altered pain perception related to biological and psychological factors may also exist simultaneously in patients with RA [1]. Of these factors, mood disorders, especially depression, have been well studied, and depression has been reported as an independent predictor of raised pain perception [2]. Another psychological disorder called alexithymia has been reported to be responsible for altered pain perception in RA [3,4]. The concept of alexithymia is characterized by the lack of emotional awareness, difficulty in describing and identifying emotions, poor fantasy life, and externally-oriented thinking [5]. The prevalence of alexithymia among adults is approximately 10% [6], however it ranges from 34% to 100% among mixed chronic pain samples [5]. Among RA patients, the prevalence of alexithymia was reported to be higher than that of healthy individuals. Moreover, the patients with higher alexithymia scores were those with greater functional impairment [7].

Beyond the pain intensity, determining the disease activity correctly is one of the most important factors for RA management. As far as we know, there has been no trial assessing the association between alexithymia and disease activity in RA. In this study, we hypothesized that alexithymic patients have worse disease activity due to the impact of alexithymia on the patient-reported components [patient global assessment of disease activity (PGADA) and tender joint count (TJC)] of Disease Activity Index with 28 joints (DAS28)].

Material and Method

The study was subjected to an ethical review, and a full ethical agreement was obtained from the local research ethics committee (Decision number: 28.11.2014;5). The participants provided written informed consent to the approved protocol.

Patients

A total of consecutive 140 patients (18 male, 122 female) was evaluated for eligibility. Patients under age 18 or with a history of major depression, psychotic disorders, dementia, mental retardation, and taking drugs associated with psychiatric illness were excluded from the study. After implementing the exclusion criteria, 97 eligible female patients with established RA who met the 1987 American College of Rheumatology criteria [8] remained. They were asked to sign informed consent for participation and to complete the questionnaire items.

Measurements

Records were reviewed for sociodemographic features (age, marital status, current employment situation, and education) and also for disease duration and medication. All patients underwent a complete physical examination, including TJC and swollen joint count (SJC). The physical examination of the patients was performed by the same clinician. The C-reactive protein (CRP) level was measured using the nephelometric method, and the erythrocyte sedimentation rate (ESR) values were determined by the Westergren method. PGADA was determined by using the 0 mm-100 mm visual analogue scale (VAS). Disease activity was determined by DAS28 using ESR (DAS28-ESR). The validated threshold values of DAS28-ESR were used to determine the disease activity state (2.6 for remission, 3.2 for low disease activity, and 5.1 for high disease activity) [9]. Disease activity score in 28 joints attributable to patient-reported components (TJC and PGADA), abbreviated as the DAS28-P index, was calculated as the ratio of the fraction of the total DAS28-ESR score contributed by TJC and PGADA to total DAS28-ESR score as follows:

$$\text{DAS28-P}= \frac{(0.56x\sqrt{TJC})+ (0.014xPGADA)}{(0.28x\sqrt{SJC})+(0.56x\sqrt{TJC})+(0.7x\ln(ESR))+(0.014xPGADA)}$$ [10].

Pain severity was determined using the 0–100 mm VAS. Blood sampling, clinical assessment, and the self-administered questionnaires were completed within the same day.

Psychological evaluation

After the physical examination, each patient was instructed by a psychiatrist in a designated room. Alexithymia was evaluated using the Turkish validated version of the 20-item Toronto Alexithymia Scale (TAS-20) in which the total score ranges from 20 to 100 with a threshold score of 61 for the alexithymia screening [11]. For the original version of the scale, scores above 60 indicate the presence of alexithymia and scores less than 52 indicate definite absence of alexithymia. Scores from 52 to 60 indicate a tendency toward alexithymia [12]. TAS-20 consists of three factorially determined scales in which each item is rated on a five-point Likert scale. Alexithymia has been found to have a three-factor structure represented by three subscales: difficulty in identifying feelings, difficulty in describing feelings, and externally-oriented thinking. Difficulty in identifying feelings scale is an index of respondents' difficulty in identifying an experience as an affective state or in distinguishing affects from accompanying bodily sensations. The difficulty in describing feelings evaluates the capacity to name the feelings verbally. The externally-oriented thinking scale reflects the tendency to relate more strongly to objective events than to psychological processes [12]. After filling out the questionnaire, each patient was assigned either to the alexithymia group or to the non-alexithymia group; the latter consisted of individuals who had been accepted as normal in terms of alexithymia according to the threshold score of 61. Subsequently, the non-alexithymia group was divided into three subgroups according to tertile values as high-normal, middle-normal, and low-normal TAS-20 score groups [13]. As far as we know, there is no established threshold point for definite absence of alexithymia and the presence of possible alexithymia for Turkish populations. In our study, the fundamental reason to divide the non-alexithymia group into three subgroups was to examine the patients who were not alexithymic but likely to have alexithymia.

The Turkish validated version of the Beck Depression Inventory (BDI), a 21-item self-administered measure, was used to assess the depressive symptom severity [14]. Each item was scored between 0 and 3 points. A high level of BDI scores indicates a high level of depressive symptom severity.

Statistical assessment

Statistical Package for Social Sciences (SPSS) for Windows (IBM Corp., Armonk, NY, USA, version 21.0) was used in the statistical evaluation. The normality of the distribution of the numerical variables was evaluated with the Shapiro-Wilk test. Differences across groups for numerical variables were tested using the analysis of variance (ANOVA) or the Kruskal-Wallis test, as appropriate. If Kruskal-Wallis test results were significant, Mann-Whitney U test was used to explore the differences between the groups. The chi-square test was used for categorical data. Spearman's correlation coefficient was used for correlation analysis. The p-value of <0.05 was considered to be significant.

Results

Demographic and clinical characteristics of patients

A total of 97 female RA patients completed the self-assessment questionnaire and participated in the study. Among the sample, 28 were alexithymic (28.8%). Alexithymic RA patients did not differ from non-alexithymic RA patients in terms of age, years of education, marital status, working status, CRP levels, pain severity, steroid use, and biological agent use (p>0.05). Disease duration was significantly higher in the lower-normal TAS-20 score group than those in the middle-normal TAS-20 score group and alexithymic group. BDI score was significantly increased from low TAS-20 scores to high TAS-20 scores. (Table 1).

Comparison of disease activity across the TAS-20 score groups

Alexithymic RA patients did not differ from non-alexithymic RA patients in terms of ESR levels, SJC (p>0.05). Median TJC was higher in alexithymics than those in other groups (p=0.003). Median PGADA and mean DAS28-ESR were significantly higher in alexithymics than those in low-normal TAS-20 score group (p=0.004, p=0.004, respectively). The frequency of high disease activity (HDA) was also significantly higher in alexithymics (p=0.038). The DAS28-P index was significantly higher in alexithymics than those in low-normal and middle-normal TAS-20 score groups (p=0.001, p=0.015, respectively) (Table 2).

Correlation analysis

A positive correlation was found between the TAS-20 and TJC, PGADA, and DAS28-P. In addition to TJC, PGADA, and DAS28-P, the BDI was also positively correlated with SJC as distinct from TAS-20. The correlation coefficient between TAS-20 and BDI was 0.567 (p<0.01). While there was a weak but significant correlation between the BDI and VAS for pain, TAS-20 was not correlated with VAS for pain. DAS28-ESR was significantly correlated with its domains and with pain severity, TAS-20 score, and BDI score. DAS28-P was strongly correlated with its subunits and VAS for pain. Both TAS-20 and BDI was positively correlated with DAS28-P. CRP was weak, but significantly correlated with DAS28-ESR, SJC, PGADA, and pain severity (Table 3).

Relationship between alexithymia and pain severity

The pain severity did not show significant differences across the TAS-20 score subgroups (p=0.210). VAS for pain was also not correlated with TAS-20. However, the BDI score, which was positively correlated with pain severity, had a tendency to be higher as the TAS-20 score increased (Table 1 and Table 3).

Discussion

It is of great importance to determine the disease activity correctly in patients with rheumatoid arthritis for the correct treatment decision as well as for assessing the treatment response. The majority of composite indices used for determining

Table 1. Demographic and clinical characteristics of the study population, according to the TAS-20 categories

	Total	TAS-20 score groups				
		Low-normal N=24	Middle-normal N=22	High-normal N=23	Alexithymic N=28	p
		<37	37-46	47-60	>60	
Age, median (IQR), years	55 (47-60)	56 (49-61)	51 (43-60.3)	53 (47-59)	55.5 (48.3-60.8)	0.503
RA disease duration, mean ±SD, years	11.2±8.0	14.8±8.6*	8.6±6.7	12.8±8.9	8.7±6.1	0.009
Education, median (IQR), years	5 (4-5)	5 (0.5-5)	5 (5-5)	5 (5-5)	5 (2.5-5)	0.600
Marital status, n(%)						0.549
Single	18 (18.6)	7 (29.2)	4 (18.2)	3 (13)	4 (14.3)	
Married	79 (81.4)	17 (70.8)	18 (81.8)	20 (87)	24 (85.7)	
Working, n(%)	13 (13.4)	1 (4.2)	4 (18.2)	4 (17.4)	4 (14.3)	0.470 0.998•
CRP, median (IQR), (mg/L)	4.8 (2.3-12.5)	5.4 (2-9.3)	5.9 (2.7-20.9)	3.9 (2-12.9)	4.9 (2.3-11.9)	0.829
VAS, pain, median (IQR), (mm)	50 (20-70)	40 (0-62.5)	50 (10-70)	45 (25-70)	50 (40-83.8)	0.210
BDI score, median (IQR)	10 (6-18)	3.5 (2-9.3)	9 (5.8-15.8)†	11 (7-23)ᵇ	17 (11.5-24)◊	<0.001
Medication						
Steroid use, n(%)	39 (40.2)	9 (37.5)	8 (36.4)	8 (34.8)	14 (50)	0.658
Biologic use, n(%)	17 (17.5)	5 (20.8)	4 (18.2)	4 (17.4)	4 (14.3)	0.942

BDI Beck depression inventory, CRP C-reactive protein, IQR Inter-quartile range, RA rheumatoid arthritis, SD standard deviation, TAS-20 Toronto 20 alexithymia score, VAS visual analogue scale

*The mean disease duration was significantly higher in low-normal TAS-20 score group than middle-normal TAS-20 score group and alexithymic group (p=0.032, p=0.024, respectively)

†The median BDI score was significantly higher in middle-normal TAS-20 score group than low-normal TAS-20 score group (p=0.005)

ᵇ The median BDI score was significantly higher in high-normal TAS-20 score group than low-normal TAS-20 score group (p<0.001)

◊The median BDI score was significantly higher in the alexithymic group than low-normal, middle-normal and high-normal TAS-20 score groups (p<0.001, p=0.001, p=0.036, respectively)

• When patients were categorized as alexithymic or not

Table 2. Comparison of disease activity and its domains, and DAS28-P across TAS-20 score groups

	Total	TAS-20 score				
		Low-normal N=24	Middle-normal N=22	High-normal N=23	Alexithymic N=28	p
		<37	37-46	47-60	>60	
ESR , median (IQR), (mm/h)	33 (18-49.5)	29.5 (13.5-43)	36.5 (27.8-53.8)	34 (12-54)	30 (19.8-40.5)	0.478
TJC, median (IQR)	4 (1-10.5)	1 (0-7)	2 (0-10.5)	4 (1-9)	8 (2.3-17)[b]	0.003
SJC, median (IQR)	0 (0-2)	0 (0-1.8)	0 (0-3)	0 (0-2)	1 (0-2.8)	0.467
PGADA, median (IQR), (mm)	50 (20-65)	35 (0-50)	50 (38.8-70)	40 (20-60)	55 (40-80)§	0.021
DAS28-ESR, mean±SD	4.3±1.5	3.7±1.7	4.4±1.6	4.1±1.1	5.1±1.2‡	0.007
Remission, n(%)	14 (14.4)	8 (33.3)	3 (13.6)	2 (8.7)	1 (3.6)	0.055
LDA, n(%)	11 (11.3)	4 (16.7)	2 (9.1)	3 (13)	2 (7.1)	
MDA, n(%)	39 (40.2)	7 (29.2)	10 (45.5)	12 (52.2)	10 (35.7)	0.038•
HDA, n(%)	33 (34.0)	5 (20.8)	7 (31.8)	6 (26.1)	15 (53.6)	
DAS28-P, median (IQR)	0.41 (0.29-0.50)	0.30 (0.0-0.45)	0.42 (0.28-0.46)	0.39 (0.29-0.52)#	0.47 (0.38-0.57)∞	0.003

DAS28-ESR disease activity score with 28 joints using erythrocyte sedimentation rate, DAS28-P disease activity score in 28 joints attributable to patient-reported components, ESR erythrocyte sedimentation rate, HDA high disease activity, IQR inter-quartile range, LDA low disease activity, MDA middle disease activity, PGADA patient global assessment of disease activity, RA rheumatoid arthritis, SD standard deviation, SJC swollen joint count, TAS-20 Toronto 20 alexithymia score, TJC tender joint count
[b] The median TJC was significantly higher in the alexithymic group than low-normal, middle-normal and high-normal TAS-20 score groups (p= 0.001, p=0.019 and p=0.021, respectively).
§ The median PGADA score was significantly higher in the alexithymic group than low-normal TAS-20 score group (p=0.004).
‡ The mean DAS28-ESR score was significantly higher in the alexithymic group than low-normal TAS-20 score group (p=0.004).
# The median DAS-P index score was significantly higher in high-normal TAS-20 score group than low-normal TAS-20 score group (p=0.047)
∞ The median DAS-P index score was significantly higher in the alexithymic group than low- normal and middle-normal TAS-20 score groups (p=0.001 and p=0.015, respectively
• When patients were categorized as alexithymic or not

Table 3. Correlation matrix

	CRP	ESR	TJC	SJC	PGADA	DAS28-ESR	DAS28-P	VAS, pain	BDI score	TAS-20 score
CRP	-	-	-	-	-		-	-	-	-
ESR	0.505**	-	-	-	-		-	-	-	-
TJC	0.211	0.149	-	-	-		-	-	-	-
SJC	0.227*	0.192	0.536**	-	-		-	-	-	-
PGADA	0.249*	0.123	0.632**	0.386**	-		-	-	-	-
DAS28-ESR	0.376**	0.431**	0.906**	0.652**	0.741**	-	-	-	-	
DAS28-P	0.079	-0.125	0.880**	0.341**	0.772**	0.742**	-	-	-	-
VAS, pain	0.250*	0.153	0.620**	0.427**	0.843**	0.711**	0.707**	-	-	-
BDI score	0.153	0.086	0.377**	0.252*	0.313**	0.354**	0.404**	0.335**	-	-
TAS-20 score	0.001	0.054	0.380**	0.165	0.260*	0.343**	0.374**	0.198	0.567**	-

BDI Beck depression inventory, CRP C-reactive protein, DAS28-ESR disease activity score with 28 joints using erythrocyte sedimentation rate, DAS28-P Disease Activity Score in 28 joints attributable to patient-reported components, ESR erythrocyte sedimentation rate, PGADA patient global assessment of disease activity, SJC swollen joint count, TAS-20 Toronto 20 alexithymia score, TJC tender joint count, VAS visual analogue scale
*Significant at 0.05 level
**Significant at 0.01 level

disease activity in RA include both questions that depend on the patient's declaration, and physical and laboratory findings. A patient's declaration about pain, TJC, and PGADA may be affected by several factors including alexithymia. Consistent with our hypothesis, the results of this study showed that having alexithymia might have an impact on disease activity by affecting the patient-reported components of DAS28-ESR.

The association between alexithymia and pain intensity may be ambiguous. The studies that included people with clear medical diseases with chronic pain such as neuromuscular disease and cancer reported that there was a significant relationship between pain intensity and alexithymia [15,16]. Regarding RA, Vadacca et al. [17] reported no relationship between alexithymia and pain severity, and Kojima et al. [3] stated that the positive association between TAS-20 and pain severity lost significance after controlling for BDI-II score and CRP level. Some studies that included people with non-specific pain problems also reported no significant association between alexithymia and pain intensity [18,19]. The underlying mechanism of the non-association between TAS-20 and pain severity in patients with arthritis might be related to higher levels of pain and racial differences as well [17,20]. In people with alexithymia, the difficulty in describing and identifying the feelings may have a negative effect on their determination of the pain intensity. Further studies are necessary to explain the causal relationship between alexithymia and pain intensity. Moreover, the variability of the alexithymia according to the treatment and the change in pain intensity should be investigated. Although alexithymia didn't correlate with pain, the significantly positive correlation between alexithymia and DAS28-ESR and DAS28-P suggests that the relationship between alexithymia and high disease activity may be related to factors other than pain.

As the formula of DAS28-P is the proportion of patient self-reported items to the whole DAS28, the higher DAS28-P score may arise from the high PGADA and TJC. On the other hand, low SJC and ESR may result in a higher DAS28-P score by decreasing the divisor of the equation. That is, a high DAS28-P may suggest noninflammatory pain. Pain is the most important determinant of PGADA [21]. PGADA may also be affected by the patient's mood [22]. In our study, PGADA was strongly correlated with pain severity and weakly correlated with BDI. Although TAS-20 was not associated with pain severity directly, the relationship of alexithymia with depressive symptom severity may be an indirect indicator of pain severity. Other than the

pain, structural damage and additional comorbidities that have not been accounted for in the present study might have effects on PGADA.

Joint tenderness is a subjective sign that is dependent upon the pain threshold and the strength of pressure applied [23]. Alexithymia may be associated with an enhanced sensitivity to unpleasant stimuli, suggesting a general hypersensitivity [24], but those with alexithymia may be insensitive to their own physical sensation when the external stimuli are not strong enough [4]. While there were no differences across the TAS-20 subgroups in terms of expressed pain intensity, meaningful high median TJC in alexithymic patients might be related to hypersensitivity to palpation in our study population. The mechanism of hypersensitivity to painful stimulation in patients with alexithymia is unknown. Dysfunction in the limbic system and negative affectivity are two of the suggested mechanisms [4].

Interestingly, mean disease duration was significantly higher in the low-normal TAS-20 score group than in the middle-normal TAS-20 score group and in the alexithymic group. Although the frequency of alexithymia can be expected to increase as the disease duration increases, Porcelli et al. [25] reported that there was no relationship between disease duration and alexithymia in the autoinflammatory disease inflammatory bowel disease (IBD). We could not find a logical explanation of our result and we thought it was accidental. New studies are needed to understand whether there is a relationship between the disease duration and alexithymia.

Our study has some limitations. First of all, the sample size was small. Patients were assessed at a single time point. The RA duration of the study sample was heterogeneous. We assessed the psychological factors using self-assessment questionnaires that might be misunderstood by patients with low levels of education. Because female gender is also a predictor of higher self-reported pain in RA [26], the fact that the study population consisted only of females was another limitation. Since our data were not appropriate for regression analysis and/or path analysis, we could not perform robust relationship analysis between alexithymia, depressive symptom severity, and disease activity.

In conclusion, in patients with high disease activity, higher pain severity, high TJC, and high PGADA but low SJC and inflammation marker levels, physicians should keep in mind the confounding factors, including alexithymia. In alexithymic RA patients, the usage of patient-reported components of disease activity indices may lead to misjudgment of disease activity. Analyzing the relationship between the alexithymia and each of the subjective components of disease activity indices by adding other confounding factors may provide additional information in the management of RA.

Competing interests

The authors declare that they have no competing interests.

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